PHARMACOPOEIA MONOGRAPHS

INTRODUCTION

- Pharmacopoeia, pharmacopeia, or pharmacopoea (literally, "drug-making"), in its modern technical sense, is a book containing directions for the identification of compound medicines, and published by the authority of a government or a medical or pharmaceutical society. Descriptions of preparations are called monographs.

- Monographs are based on the specifications for substances used in medicinal products approved in Member States. When a monograph is added to the work programme, enquiries are made by the EDQM to identify manufacturers of such substances and all data received is taken into account for preparation of the monograph. Interested parties should be invited to participate in the elaboration of the monograph before publication in Pharmeuropa, since the 3-month public period will often be too short for all interested parties to check the draft monograph.

- Prior to the preparation of any monograph, it is essential to gather as much information as possible on the substance in question.

In particular it is necessary to ascertain:

- ● whether the substance is of natural, synthetic or semi-synthetic origin;
- ● whether the substance is a mixture or a single entity;
- ● the method(s) of preparation in detail;
- ● whether there are different crystalline forms, since the properties of the substance may vary in accordance with this parameter
- whether both an enantiomer as well as the racemate or other mixtures of enantiomers are available;
- ● whether different hydrates are available;
- ● whether different entities (acid, base, salt, etc) are available

- The Pharmacopoeia and other relevant documents on the state of work must be consulted to see if monographs on similar substances exist or are being elaborated.
- If monographs or draftson similar substances already exist, it is important to ensure that the monograph to be elaborated follows the same approach unless there are good reasons to deviate, e.g. developments in analytical techniques.
- Substances that are to be described in a monograph may be members of a group of very similar substances (family). This holds true especially for excipients such as macrogols.

TITLE

- The International Nonproprietary Name (INN) established by the World Health Organization should be used wherever it is available; it is supplemented as appropriate by the name of the anion or cation and by “hydrate”, “dihydrate”, “hydrated” (for ill-defined degrees of hydration) or “anhydrous” (where a hydrated form is also known to exist).
- Formerly, the degree of hydration was not indicated in titles unless 2 forms were known to be available;
- existing titles of this type are not changed on revision unless it is known that 2 forms are available or if there is a public health imperative (for example, high water content that could lead to errors in formulation).
- Anions and cations are indicated as “mono-”, “di-”, “tri-”, etc., as appropriate.
- Where a substance is used in approved medicinal products for veterinary use only in Member States, “for veterinary use” is included in the title.

DEFINITION

- The chemical structure must be ascertained with the greatest possible precision in order to establish the exact:
- □ graphic formula;
- □ empirical formula and relative molecular mass
- chemical name

-This implies investigating in particular:

- the possible existence of isomers so as to be able to specify which isomer is used or, otherwise, to state that the product is a mixture of isomers;
- in the case of an optical isomer, it is insufficient to take into account only the direction of the optical rotation. The absolute configuration is given by the *R*/*S* system at the asymmetrical centre(s) or any other appropriate system (e.g., for carbohydrates and amino acids);
- ascertaining the state of hydration or solvation so as to distinguish clearly between the well-defined hydrates and solvates and the products that contain variable quantities of solvent(s).

COMBINATIONS

- In therapeutics, more or less well-defined chemical combinations (for instance, theophyllineethylenediamine) or even mixtures are sometimes used.
- In such cases, it is necessary to specify precisely each component of the combination or mixture, with its chemical structure and the proportion in which it is present.

CONTENT

- The substance described by a monograph is never a wholly pure substance but contains a limited proportion of impurities. The content is therefore an important part of the definition.
- Assay limits are specified between which the content must fall.
- The assay limits must take account of the precision of the method as well as the acceptable purity of the substance. Assay limits are normally expressed with reference to the dried or anhydrous substance
- For a non-specific assay (for example, titrimetry) the assay limits are usually 99.0-101.0 % (unless otherwise justified).
- For a specific assay using a separation technique (for example, liquid or gas chromatography), the upper assay limit is normally 102.0 %; the lower assay limit will take any necessary account of the impurities present and may therefore be lower than 98.0 %.

CHARACTERS

1. APPEARANCE

This description will normally embrace color and physical form.

2. TASTE

The taste is not to be taken into consideration

3. ODOUR

In general, no reference is made to odor

4. SOLUBILITY

- Solvents quoted are normally confined to water, an alcohol and a lipophilic solvent. Solubility in chloroform and ether are not mentioned. In special cases the solubility of different samples of a material may vary rather considerably even though their composition is still within the limits set by the monograph. The solubilities in the solvents thereby affected are then given to cover more than one solubility class, e.g. “sparingly soluble to soluble in...”. The solubility or miscibility in other solvents with which the material is often combined in practice such as fatty oils, etc., may also be mentioned.

CHARACTERS

5. Stability factors

- Evidence of instability due to exposure to air, light and for moisture is to be given, e.g. physostigmine sulfate turns red when exposed to air and light.

6. Hygroscopicity

- A pragmatic method recommended for the determination of the tendency of a substance to take up atmospheric water
- Some substances are hygroscopic or deliquescent, which results in difficulties for the analyst during weighing procedure

CHARACTERS

7. Solid-state properties

- Solid-state properties include crystallinity, polymorphism, density of solids, particle size of solids and specific surface area of solids. Solid-state properties, particularly polymorphism and pseudopolymorphism, may have an effect on the bioavailability of the substance and for the production of the medicinal product
- Two cases are to be distinguished when polymorphism is known to exist:
- □ usually, the monograph does not exclude any of the possible crystalline forms;
- □ exceptionally, if the substance is only used in solid dosage forms and one form has been shown to be preferred from the point of view of bioavailability or to have a better safety/efficacy profile, then the monograph may be limited to that form.

CHARACTERS

8. Other characteristics

- -Melting point (insufficiently precise to allow a range to be quoted)
- When decomposition may occur, this must be stated.
- Other general characteristics that may be of relevance for quotation include an indication of direction of optical rotation in a particular solvent or, in the case of radioactive materials, a note of the half-life of the radionuclide defined and of the type of radiation that it emits.

9. Behavior in solution

- In cases where it is known that rapid degradation may occur in solution, this information is given as a warning statement.

IDENTIFICATION

- The purpose of the IDENTIFICATION section of a monograph is to provide confirmation of the identity of the substance in question. Identification according to the Pharmacopoeia is thus generally of a much more limited scope than the structural elucidation of an unknown substance or the determination of the composition of an unknown mixture.
- The task of identifying a material is not to be confused with the assessment of its purity or the determination of its strength, although ultimately all 3 aspects are complementary.
- It follows from the above that the physical and/or chemical tests and reactions, when taken together, that enter into the IDENTIFICATION section ensure, as far as possible, specificity.
- The specificity of the identification should be such that active substances and excipients exhibiting similar structures are distinguished.

IDENTIFICATION

Methods requiring complex instrumentation

- Spectrophotometric analysis, such as recording of infrared or nuclear magnetic resonance spectra.
- Chromatographic examination by means of gas chromatography (GC) or liquid chromatography (LC).

Other methods

- Determination of physical constants such as melting point, freezing point, boiling point, specific optical rotation, angle of rotation, ultraviolet spectrum, specific absorbance, relative density, refractive index and viscosity.
- Chemical reactions such as color or precipitation reactions (including formation of derivatives or degradation products, which may subsequently be subjected to physical examination) and determination of chemical values (saponification, ester, hydroxyl and iodine values).
- Chromatographic examination by thin-layer chromatography (TLC).

TESTS

Solution S

- A solution of the substance to be examined, designated “Solution S”, is prepared whenever this can be used to perform more than one test (and/or identification).
- If necessary, several solutions S, (designated S1, S2...) may be prepared in various ways, each being used for at least 2 tests.
- For insoluble substances, solution S may be prepared by an extraction process.
- The solvent used depends on the solubility of the substance to be examined and that of its potential impurities. It may be:
- water (usually):
- o carbon dioxide-free water in cases where the presence of carbon dioxide can appreciably influence the outcome of a test, e.g. for pH or Acidity or alkalinity

o distilled water if solution S is used in the tests for barium, calcium and sulfates;

- o carbon dioxide-free water prepared from distilled water when both aforementioned considerations apply;
- a dilute acid or an alkaline solution;
- more rarely, other solvents (alcohols, tetrahydrofuran...) that give solutions with a narrower field of application than aqueous solutions.

TESTS

Solution S

- The solvent used and the concentration chosen depend on the solubility of the substance to be examined and the purpose for which the test is intended. The solvent must make it possible to carry out the specified tests, either directly, or after suitable dilutions explicitly specified in each test.
- Generally the concentration is around 20 to 50 g/L but may be lower (e.g. 10 g/L) or higher (100 g/L and, exceptionally, more). The quantity of solution S prepared must be sufficient to carry out each of the tests for which it has been prepared. If solution S is to be filtered, account must be taken of the loss on filtering and when the insoluble portion thus separated is to be used for another test, this is clearly indicated.
- If several tests can be carried out on the same portion of solution S, this is only done for substances where there are good reasons to economise (expensive products or products whose use is subject to restrictions) and this is then clearly indicated in the monograph.

TESTS

Solution S

- Depending on the particular tests, the concentration of solution S is defined with varying precision:
- for “Appearance of solution”, “pH” and some identifications, a precision of 5 to 10 % is sufficient;
- for most limit tests a precision of about 2 % is appropriate;
- for some cases such as the determination of specific rotation, specific absorbance, various chemical values and, more generally, tests where the result is obtained by calculation, a greater precision is needed.

TESTS

Solution S

- The precision with which the concentration of solution S is defined is that required by the most exacting test for which it is intended.
- The description of the preparation of solution S thus specifies:
- the quantity of substance to be examined with the required precision
- the volume, to 1 decimal place (10.0 mL, 25.0 mL...) when the concentration must be known to within less than 1 %, without a decimal (10 mL, 25 mL...) when a lower precision is adequate.

TESTS

Appearance of solution

- This test makes it possible to ascertain the general purity of a substance by the detection of impurities insoluble in the solvent selected, or of coloured impurities.
- The “Appearance of solution” test is practically always prescribed for substances intended for preparations for parenteral use. Apart from this, it is to be applied only if it yields useful information concerning the general purity of the substance.
- It can comprise both tests or one only, namely:
- □ clarity and degree of opalescence of liquids
- □ degree of coloration of liquids

TESTS

Appearance of solution

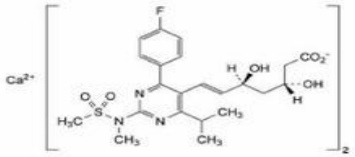
- The 2 tests are practically always carried out on identical solutions, usually solution S, but they may be performed on different solutions.
- The solvent employed is usually water but other solvents may be preferred depending on the solubility of the substance to be examined.
- When an organic solvent is used to prepare solution S, it may be necessary to ensure that the solvent also complies with the test, especially where there is a very stringent requirement.
- The more concentrated the solution the stricter the test. For very pure substances or those used in high doses, the concentration chosen is 50 to 100 g/L, whereas for less pure substances or substances administered in small doses the concentration is 10 to 20 g/L.

Reference: PA/PH/Exp. P4/T (11) 36 ANP

XXXX:2631

ROSUVASTATIN CALCIUM

Rosuvastatinum calcicum



$C_{44}H_{54}CaF_2N_6O_{12}S_2$ M_r 1001
[147098-20-2]

DEFINITION

Calcium bis[(3*R*,5*S*,6*E*)-7-[4-(4-fluorophenyl)-2-[methyl(methylsulfonyl)amino]-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoate].

Content: 97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, hygroscopic powder.

Solubility: slightly soluble in water, freely soluble in methylene chloride, practically insoluble in anhydrous ethanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *rosuvastatin calcium CRS*.

B. Enantiomeric purity (see Tests).
Results: the principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (c).

C. It gives reaction (b) of calcium (*2.3.1*).

TESTS

Related substances. Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Test solution. Dissolve 35.0 mg of the substance to be examined in 12 mL of *acetonitrile for chromatography R* and dilute to 50.0 mL with *water for chromatography R*.

Reference solution (a). Dissolve 35.0 mg of *rosuvastatin calcium CRS* in 12 mL of *acetonitrile for chromatography R* and dilute to 50.0 mL with *water for chromatography R*.

Reference solution (b). To 1.0 mL of the test solution add 24 mL of *acetonitrile for chromatography R* and dilute to 100.0 mL with *water for chromatography R*. To 2.0 mL of this solution add 2 mL of *acetonitrile for chromatography R* and dilute to 10.0 mL with *water for chromatography R*.

Reference solution (c). In order to prepare impurity B *in situ*, dissolve 10 mg of the substance to be examined in 10 mL of a 1 per cent *V/V* solution of *trifluoroacetic acid R* in *acetonitrile for chromatography R*. Stopper and heat at 40 °C for 1 h. Cool, add 20 mL of *water for chromatography R* and adjust to pH 6-8 with a 42 g/L solution of *sodium hydroxide R*. Dilute to 50 mL with *water for chromatography R*.

Reference solution (a). Dissolve 5 mg of *rosuvastatin impurity A CRS* in 10 mL of *acetonitrile for chromatography R* and dilute to 20.0 mL with *water for chromatography R*.